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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/635,241 | 08/05/2003 | Zhen Zhang | 58369 (71699) | 6657 |
| 21874 | 7590 | 02/28/2006 | EXAMINER | |
| EDWARDS & ANGELL, LLP P.O. BOX 55874 BOSTON, MA 02205 | | | MILLER, MARINA I | |
| | | ART UNIT | | PAPER NUMBER |
| | | | | 1631 |
| DATE MAILED: 02/28/2006 | | | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

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|------------------------------|-----------------|--------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/635,241 | ZHANG ET AL. |
| | Examiner | Art Unit |
| | Marina Miller | 1631 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 18 November 2005.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 112-220 is/are pending in the application.
 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) See Continuation Sheet is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

| | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. <u>1 copy</u> . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Applicants' submission filed on 11/18/2005 is acknowledged. Claims 112-220 are pending. Claims 1-111 are cancelled.

Claims 119, 121-122, 125-126, 128-130, 135-136, 140, 154-156, 159-160, 162-164, 169-170, 174, 179, 193-195, 198-199, 201-203, 208-209, 213, and 218 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claims.

An action on the merits of claims 112-118, 120, 123-124, 127, 131-134, 137-139, 141-145, 147-153, 157-158, 161, 165-168, 171-173, 175-178, 180-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 219-220, as they read on the elected species, follows.

Applicants' arguments have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are applied.

Claim Rejections - 35 USC § 112

First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 112-118, 120, 123-124, 127, 131-134, 137-139, 141-145, and 147-148 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification

in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claims 112 recites in step (d) substep (iii) samples coming from populations having “a statistically significant difference with respect to … preanalytical variables.” Applicants do not point to support for the limitation in the originally filed application. The specification discloses data elements identified with high confidence values (a selected difference from a null (randomized) distribution being accepted as statistically significant, *e.g.*, $p \leq 0.01$). The originally filed application does not provide support for statistically significant difference for preanalytical variables (*e.g.*, age, weight, diet, gender, *etc.*) which may or may not be the same as for the data elements (*e.g.*, gene expression data). For the reason stated above, the instant claims are rejected for introducing new matter.

Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 112-118, 120, 123-124, 127, 131-134, 137-139, 141-145, 147-153, 157-158, 161, 165-168, 171-173, 175-178, 180-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 219-220 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 112 recites the limitation “the data from each sample” in substep (ii) of step (a).

There is insufficient antecedent basis for this limitation in the claim. Claim 112 recites in step (a) “first data from a first set of samples.” Thus, “first data” is derived from a set of samples while “the data” is derived from a sample, and therefore different from the earlier recited “first data.” As the intended limitation is not clear, claims 112-118, 120, 123-124, 127, 131-134, 137-139, 141-145, and 147-148 are indefinite.

Claim 112 recites the limitation “the data from each sample” in substep (ii) of step (d).

There is insufficient antecedent basis for this limitation in the claim for the reasons stated above for step (a). As the intended limitation is not clear, claims 112-118, 120, 123-124, 127, 131-134, 137-139, 141-145, and 147-148 are indefinite.

Claim 112 recites the limitation “to qualify each common data element … based on the ability … to classify a sample … as a function of data element value” in steps (b) and (e). It is not clear whether the limitation “as a function of data element value” relates to the limitation “to qualify” or the limitation “to classify.” As the intended limitation is not clear, claims 112-118, 120, 123-124, 127, 131-134, 137-139, 141-145, and 147-148 are indefinite.

Claim 112 recites in step (d) substep (iii) “the first samples and the second samples.” It is not clear whether the first and the second samples is intended to be the first and the second set of samples (see lines 2-3 and 125) or a first and a second sample in each of the first and the second sets of samples. As the intended limitation is not clear, claims 112-118, 120, 123-124, 127, 131-134, 137-139, 141-145, and 147-148 are indefinite.

Claims 149 and 182 recite in step (a) the limitation “input data relating to … data sets.” The “relation” of input data to data sets is not clear because criteria of “relatedness” is not

disclosed in neither claims nor the specification, *e.g.*, input data may be composed of data sets, may comprise data sets, may be another data obtained from data sets, *etc.* Claims 150-153, 157-158, 161, 165-168, 171-173, 175-178, and 180-181 depend from claim 149. Claims 183-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 219-220 depend from claims 182. As the intended limitation is not clear, 150-153, 157-158, 161, 165-168, 171-173, 175-178, and 180-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 219-220 claims are indefinite.

Claim 182 recites the limitation “the data from each sample” in substep (ii) and (iv) of step (a). There is insufficient antecedent basis for this limitation in the claim. Claim 182 recites in step (a) “first and second data sets.” Thus, “first and second data” are derived from two the first and the second sample, and therefore different from the earlier recited “first and second data sets.” As the intended limitation is not clear, claims 182-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 219-220 are indefinite.

Claim 182 recites the limitation “to qualify each common data element … based on the ability … to classify a sample … as a function of data element value” in step (b). It is not clear whether the limitation “as a function of data element value” relates to the limitation “to qualify” or the limitation “to classify.” As the intended limitation is not clear, claims 182-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 219-220 are indefinite.

Claim Rejections - 35 USC § 102

Claims 112-117, 123-124, 127, 131-134, 137-139, 141, 143-145, and 148 are rejected under 35 U.S.C. 102(a) as being anticipated by Petricoin, *The Lancet*, 359:572-577 (February 16, 2002).

New claims 117-148 have limitations similar to those of cancelled claims 2-35. New claims 113-114 limit claim 112 to a preanalytical variable selected from a group of specific variables. New claims 115-116 limit claim 112 to the samples collected from different geographical locations and clinical trial sites, respectively.

Applicants argue that Petricoin does not disclose analysis of a first and a second set of samples separately that includes classifying samples into different biological states for each set of samples. Applicants' arguments have been considered, but are found not persuasive.

Petricoin discloses analyzing two independent sets of samples. Specifically, one "sample" is composed of 50 control samples for preliminary analysis, other 17 control samples, and samples from cancer patients for preliminary analysis (*see p. 572-573, Methods and Study Population; table 1; fig. 1, p. 575, and p. 576*). A second "sample" is composed of 50 control samples for the masked analysis, other unaffected samples, and samples -2; fig. 1, p. 575, and p. 576). Both "samples" were collected and statistically analyzed independently to classify samples into different biological states (*e.g.*, cancer and unaffected states) (fig. 1, p. 575, table 2, p. 576, left col.). The results obtained from two independent samples (preliminary and masked) were "intersected" wherein data elements (key values for classifying samples, *e.g.*, M/Z) in the intersection subset is a member of both subsets (preliminary and masked samples) (p. 576). Thus, Petricoin discloses a method recited in instant claim 112. Petricoin further discloses a preanalytical variable, *e.g.*, medical status, a clinical characteristic, medical condition (*see table 1*). Petricoin discloses samples collected at different locations (p.573). Thus, the examiner maintains that Petricoin anticipates the limitations of the instant claims.

Claim Rejections - 35 USC § 103

Claim 147 is rejected under 35 U.S.C. 103(a) as being unpatentable over Petricoin, *The Lancet*, 359:572-577 (February 16, 2002), as applied to claims 112-117, 123-124, 127, 131-134, 137-139, 141, 143-145, and 148 above, and in view of Golub, *Science*, 286:531-537 (Oct. 15, 1999).

Applicants argue that Golub teaches away from the instant method where data sets may be collected by different collection protocols. Applicants further argue that Golub does not disclose selecting an intersection subset. Applicants' arguments have been considered, but are found not persuasive.

Golub discloses range of samples, *e.g.*, bone marrow and peripheral blood samples, samples collected from children and adults, samples collected from different labs, and samples collected by different protocols (p. 532, right col., last paragraph). Although Golub states that the average prediction strength was lower for samples from one laboratory that used a very different protocol for sample preparation and suggests standardization of sample preparation, Golub does teach using different sample preparation protocols (p. 532, right col., last paragraph). Further, Golub does not discuss the reasons for the lower predictive strength for one sample and does not discuss meaning of "standardization" a protocol which does not necessarily mean using one protocol for all types of samples in all laboratories.

Although Golub is relied upon for the limitation "different collection protocols," Golub further discloses two independent samples for which data were collected separately and each was classified on the basis of data elements, *e.g.*, 38 initial leukemia samples and independently collected 34 leukemia samples (p. 532, 534). Golub also discloses comparing two samples

wherein the structure (data elements – gene predictors) in the initial sample is also seen in the independent sample (*i.e.*, samples are intersected) (p. 534, middle col. and fig. 4).

Perticoin teaches the method of claim 112, as set forth above.

Motivation to combine the references was provided in the previous office action and is reiterated below:

“It would have been obvious to one skilled in the art at the time of the invention to modify the method of Petricoin to use different collecting protocols for different data sets, as taught by Golub, where the motivation would have been to use different types of tissues/samples for constructing a model predictive of cancer for unknown samples, as taught by Golub, (p. 532, right col.).”

Claims 118, 120, 142, 149-153, 157-158, 161, 165-168, 171-173, 175-178, 181-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 220 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petricoin, *The Lancet*, 359:572-577 (February 16, 2002), as applied to claims 112-117, 123-124, 127, 131-134, 137-139, 141, 143-145, and 148 above, and in view of Barnhill, U.S. Patent 6,789,069.

The instant claims recite limitations similar to those of cancelled claims 3, 5, 29, 36-38, 40, 44-45, 48, 53-56, 59-61, 63-67, 71-79, 81, 85-86, 89, 94-97, 100-102, and 104-108.

Applicants argue that Barnhill does not disclose using two samples independently and selecting an intersection subset.

This is a rejection under 35 U.S.C. 103(a) over a combination of references. Although Barnhill discloses two independent samples (training and test samples, col. 50), Barnhill is relied

upon for the limitations discloses in claims 118, 120, 142, 149-153, 157-158, 161, 165-168, 171-173, 175-178, 181-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 220, for the same reason as set forth in the previous office action for claims 3, 5, 29, 36-38, 40, 44-45, 48, 53-56, 59-61, 63-67, 71-79, 81, 85-86, 89, 94-97, 100-102, and 104-108. Petricoin teaches an intersection subset and other limitations of the method of claim 112, as set forth above. Therefore, the examiner maintains that Petricoin and Barnhill make obvious the claimed limitations for the reasons set forth above and in the previous office action.

Claims 180 and 219 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petricoin, *The Lancet*, 359:572-577 (February 16, 2002), in view of Barnhill, U.S. Patent 6,789,069, as applied to claims 118, 120, 142, 149-153, 157-158, 161, 165-168, 171-173, 175-178, 181-190, 192, 196-197, 200, 204-207, 210-212, 214-217, and 220 above, and further in view of Golub, *Science*, 286:531-537 (Oct. 15, 1999).

Applicants did not specifically address the rejection. The examiner maintains that Petricoin teaches the method of claim 112, Golub teaches different collection protocols, and Barnhill teaches the computer program and the system recited in the instant claims, as set forth above and in the previous office action. Thus, the examiner maintains that Petricoin, Golub, and Barnhill make obvious the claimed limitations for the same reasons and motivations as previously set for claims 69 and 110.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marina Miller whose telephone number is (571)272-6101. The examiner can normally be reached on 8-5, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph. D. can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marina Miller
Examiner
Art Unit 1631

MARJORIE A. MORAN
PRIMARY EXAMINER

MM

Marjorie A. Moran
2/9/06

Continuation of Disposition of Claims: Claims withdrawn from consideration are 119,121,122,125,126,128-130,135,136,140,154-156,159,160,162-164,169,170,174,179,193-195,198,199,201-203,208,209,213 and 218.

Continuation of Disposition of Claims: Claims rejected are 112-118,120,123,124,127,131-134,137-139,141-145,147-153,157,158,161,165-168,171-173,175-178,180-190,192,196,197,200,204-207,210-212,214-217,219 and 220.